

Generic medicines – Quo vadis essential similarity?

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Ohne Unterschied macht Gleichheit keinen Spaß.
(Dieter Hildebrandt, dt. Kabarettist)

Abbreviations

ATC classification	Anatomical Therapeutic Chemical classification
BMS	Bristol-Myers Squibb Pharmaceuticals Limited
EC	European Community
ECJ	European Court of Justice
EMA	European Medicines Agency
EU	European Union
MCA	The Medicines Control Agency, UK
MHRA	Medicines and Healthcare products Regulatory Agency
UK	United Kingdom
US	United States of America

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1 Introduction

If interested laypersons or patients are nowadays searching the web for information on generic medicines, they can find a common and simplified definition on the web pages of the most generic companies: “A generic product is a medicinal product containing the same active substance as the originally patented originator product. Although being of high quality, generics can be offered to lower prices because the research costs are comparably low” (www.hexal.de, www.ratiopharm.de, www.stada.de).

This definition is surely correct as regards content and sufficient for a first patient information, but yet underestimates central questions concerning marketing authorisations for generic products, namely how similar must the active substance be to the originator’s to be considered “the same”? If this question is transferred from the active substance to the product as a whole, one faces the most contradictory question in the frame of generic medicinal product authorisation: To what degree must the generic product be comparable to the originator’s product or in other words, what is meant by “essential similarity” as it is worded in the European pharmaceutical legislation as an apparent basic requirement for the registration of a generic product. How is the term “essential similarity” interpreted and how did this interpretation as well as its relevance for the generic or abridged marketing authorisation procedure change over the last years?

In the following, a review is provided on the historical development of the legal basis for generic medicinal products. The definition and interpretation of the term “essential similarity” as developed by jurisdiction of the European Court of Justice as well as the expansion of possibilities to refer and cross-refer to original products is worked out by presenting and discussing four important law cases of the ECJ dealing with these issues. Additionally, a foresight of the new definition of generics in the light of the Review 2004 of the European pharmaceutical legislation and its impact on the generic marketing authorisation application is given.

2 Results

2.1 Development of the Pharmaceutical Market and Legislation until 1965

The roots of the pharmaceutical industry in Germany date back in the 19th century and were made possible by substantial progress in chemistry and physics which enabled the systematic investigation of drug effects. At the same time, animal experimental research was further developed and improved and aided in understanding the effect of poisons and drugs in the body and individual organs.

A first milestone in the development of the pharmaceutical industry was the isolation of pure active substances from known drugs, which were morphine from poppy seed in 1803, strychnine from Ignatius beans in 1818 and quinine from China tree in 1821. More than 100 years went by till the technique of structural analysis had developed to an extent that the molecular structure of morphine could be resolved in 1913. Further 25 years later, the substance was synthesised and was therefore one of the first chemically produced pharmacological active substances.

By this time, the production and sale of drugs was restricted to pharmacies. Due to the growing number of chemically synthesized substances which were used for the production of drugs and due to reformation of the social legislation which made medical care affordable for a broad population, the growing need for synthesized substances lead to the separation of pharmacies and pharmaceutical plants. In 1827, the first plant in Germany was started up by Heinrich Emanuel Merck, the owner of a pharmacy in Darmstadt, which was the origin of Merck Darmstadt, one of the big fishes in the chemical/pharmaceutical sector in Germany.

The progress in the dye industry had further influence on the development of the pharmaceutical industry as several intermediates in the production of aniline dyes were found to be suitable starting materials for drug synthesis. Further developments in this sector lead for example to the production of the first anti-syphilis drug Salvarsan by Bayer in 1910.

Additional milestones in the diversification of the production techniques of active substances were the isolation of insulin from pig pancreas in 1921 as well as the development of the fermentation technique for the mass production of the most significant drug in the 20th century, the antibiotic penicillin in 1941 in the US [1].

In the post-war period of 1950-1960, the pharmaceutical industry was steadily established and showed a vertically integrated structure, performing all processes from early research and

development to production, sales and marketing. By that time, neither the patent law, which was not very well developed and did not always protect the products of multinational companies because of missing international patent rules, nor the pharmaceutical law which was still in its fledgling stages kept imitators from producing copies of pharmaceutical products. Pharmaceutical legislation was a national issue and although medicinal products had to be registered in Germany since 1961 according to the first German pharmaceutical law, neither a proof of efficacy nor safety had to be submitted by the originator or imitator company to the competent Authority and the registration served rather as a control element to maintain the overview of marketed products [2].

The tragic consequences of this practice revealed by the Contergan-case showed that the legislation did not adequately safeguard public health and underlined the need for stricter control of efficacy and safety of medicinal products.

With the introduction of a common European legislative basis by means of Directive 65/65/EC [3], not only the completely diverse conditions for the marketing of pharmaceuticals in the EU member states were harmonised by subsequent implementation of the Directive in national laws, but also the proof of quality, safety and efficacy was introduced as a prerequisite for the authorisation of drugs. Article 4(8) introduced for the first time the need for submission of data generated in

- physico-chemical, biological or microbiological tests;
- pharmacological and toxicological tests and
- clinical trials,

the non-conduction of which had made the business profitable for imitator companies so far because of the substantially lower costs and shorter time for development. However, it has to be mentioned that generics as we know them today played only a minor role on the pharmaceutical market at that time, although copying of active drug substances was well known and widely spread. Nevertheless, Article 4(8)(a)(iii) of Directive 65/65 provided several loopholes for this issue in stating that

“a list of published references relating to the pharmacological tests, toxicological tests and clinical trials may be substituted for the relevant test results in the case of:

- (i) a proprietary product with an established use, which has been adequately tested on human beings so that its effects, including side-effects, are already known and are included in the published references;
- (ii) a new proprietary product, in which the combination of active constituents is identical with that of a known proprietary product with an established use;
- (iii) a new proprietary product consisting solely of known constituents that have been used in combination in comparable proportions in adequately tested medicinal products with an established use”.

This open wording and the lack of need for a comparability testing between the new and reference product did not represent a hurdle for second applicants, but enabled their applications for imitations, as long as they could provide proof of safety and efficacy in form of literature.

With the increasing impact of generic products on the pharmaceutical market and on pricing, it emerged that innovator companies at that time could not always gain enough protection of their intellectual property by patent protection for two main reasons. On the one hand, the time needed for research and development to ensure compliance with the increasing requirements for drug approval had increased in a way that the marketing period before the expiry of the patent protection was often too short to ensure appropriate profit. Especially for biological products, the patent law was not clearly regulated and therefore appropriate protection for highly innovative products was often missing.

On the other hand, national authorities tended more and more to allow reference by second applications not only to published literature as stated in the legal text, but also on data submitted by innovator companies for their applications for the respective reference product. For example, the German “Federal Health Authority” (Bundesgesundheitsamt, BGA) declared in its announcement from 30. May 1979 that it was principally possible to refer to data of original products, as long as the product was “in the frame of an existing authorisation” [4]. This practice was justified with the fact that published literature was often incomplete or inappropriate for the proof of efficacy and/or safety and that the Authority thereby aimed to avoid repetitive and therefore unnecessary animal and human testing. Additionally, the introduction of this abridged procedure with its reduced amount of submitted data presented a welcome tool for authorities to decrease the growing expenditure of labour in the review

process and to reduce the time to approval which was steadily increasing with growing numbers of applications.

For these reasons (which were also declared in a 1984 report from the Commission [5] as well as in the recitals to the below described new Directive) and under the pressure of the innovative industry which feared profound loss of profit as a consequence of a globalized competition and increasing costs for research and development, the European Commission published a substantial amendment to Directive 65/65/EC in December 1986. Directive 87/21/EC introduced for the first time a data protection period for innovative products and defined an abridged application procedure for generic products referring to an original product [6].

Article 4.8 of Directive 65/65/EC as amended by Directive 87/21/EC laid down that:

“However, and without prejudice to the law relating to the protection of industrial and commercial property:

(a) The applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate:

- (i) either that the proprietary medicinal product is essentially similar to a product authorized in the country concerned by the application and that the person responsible for the marketing of the original proprietary medicinal product has consented to the pharmacological, toxicological or clinical references contained in the file on the original proprietary medicinal product being used for the purpose of examining the application in question;

...

- (iii) or that the proprietary medicinal product is essentially similar to a product which has been authorized within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made; this period shall be extended to 10 years in the case of hightechnology medicinal products within the meaning of Part A in the

Annex to Directive 87/22/EEC (OJ No L 15, 17.1.1987, p. 38.) or of a medicinal product within the meaning of Part B in the Annex to that Directive for which the procedure laid down in Article 2 thereof has been followed; furthermore, a Member State may also extend this period to 10 years by a single Decision covering all the products marketed on its territory where it considers this necessary in the interest of public health. Member States are at liberty not to apply the abovementioned six-year period beyond the date of expiry of a patent protecting the original product.

However, where the proprietary medicinal product is intended for a different therapeutic use from that of the other proprietary medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate pharmacological and toxicological tests and/or of appropriate clinical trials must be provided. ”

In certain respects, the scope of the provisions laid down in Article 4(8) concerning the abridged application was not entirely clear and has given rise to differences in interpretation which were controversial between originator and generic side and which had only recently started to be addressed.

In particular, the seemingly simple wording of Articles 4(8)(a)(i) and (iii) (corresponding to Articles 10(1)(a)(i) and (iii) of the codified text in Directive 2001/83/EC [7]) raised several issues of interpretation which had been brought to many national courts as well as the European Court of Justice:

- What is meant by essential similarity?
- Is a line extension (e.g. an additional strength or pharmaceutical form) of an original product eligible to a further independent period of protection?
- Under which circumstances is the proviso after Article 4(8)(a)(iii) applicable and what is the extent of bridging data to be provided with the application under this provision?

In the following chapters, four cases assessed by the European Court of Justice which had substantial influence on the common legislative practice of abridged applications in the European Union are presented and analysed.

2.2 The Generics Case – the decision of the European Court of Justice on the definition of essential similarity (Case C-368/96) [8]

The open language in Directive 65/65/EEC regarding the circumstances in which a second or subsequent applicant is not required to provide the results of preclinical tests or clinical trials resulted in many legal cases which explored the rights of the innovator company vs. the generic applicant. Of particular relevance is the landmark case C-368/96 in which the meaning of “essential similarity” was defined by the European Court of Justice in December 1998.

2.2.1 The Dispute

Three national cases came up between 1993 and 1995 in the UK dealing with applications for marketing authorisations for generic products according to Article 4.8 (a) (iii) of Directive 65/65/EEC (as amended by Directive 87/21/EEC).

The first case pertained the submission of an abridged application of Generics (UK) Limited (‘Generics’) for Captopril in 1993, which is a medicinal product developed by Bristol-Myers Squibb Pharmaceuticals Limited (in the following ‘BMS’) and first authorised in Germany in 1981. The originally authorized indication for this product was treatment of severe hypertension. After considerable further development and research involving substantial costs, BMS obtained new marketing authorisations for the new indications for myocardial infarction and diabetic nephropathy. The British licensing Authority MCA (The Medicines Control Agency) in a first decision agreed to grant a generic authorisation for captopril in respect of indications which had been authorised for more than 10 years, which is the extended period of data protection granted in UK, but refused to grant the authorisation for any indication which had not been approved for at least 10 years. After Generics had referred the matter to the English High Court of Justice, the MCA decided to grant the authorisation for the indication of myocardial infarction, but not for diabetic nephropathy. As reasons for this decision, the MCA relied on a policy that focused on whether a variation (in this particular case a new indication) represented a major change to a product such that, under Annex II to Commission Regulation (EC) No. 541/95 [9], a new application would be required. This text provides that

“Certain changes to a marketing authorization have to be considered to fundamentally alter the terms of this authorization and therefore cannot be considered as a variation in the meaning of Article 15 of Directive 75/319/EEC or in the meaning of Article 23 of Directive 81/851/EEC. For these changes, listed below, an application for a new marketing authorization must be made.

The respective changes included

“2. *Changes to the therapeutic indications* (Therapeutic indication is defined as the third level of the Anatomical Therapeutic Chemical (A.T.C./A.T.C. Vet) code):

- (i) addition of an indication in a different therapeutic area, either treatment, diagnosis or prophylaxis;” [...]

In the MCA’s opinion, the indication for diabetic nephropathy fulfilled these conditions; therefore the Authority was not willing to approve it, whereas it accepted the use of the abridged procedure for the indication of myocardial infarction¹.

The second proceeding dealt with the marketing authorisation obtained by A/S Gea Farmaceutisk Fabrik (‘Gea’) for all therapeutic indications and dosage forms of Acyclovir tablets and intravenous infusion for which the originator company Wellcome Foundation Limited (‘Wellcome’) had obtained authorisation in the UK between 1981 and 1994. Wellcome intervened by asking for judicial review of the MCA’s approval of the indications and dosage forms which had been approved in the Community for less than 10 years.

The third case concerned by the ECJ judgement involved ranitidine, a medicinal product of Glaxo Operations UK Ltd (‘Glaxo’) authorised in the UK between 1981 and 1995. Equally to the above mentioned proceeding, the MCA considered that the second applicant Generics could rely on the abridged procedure for all indications, doses and dosage forms even if authorised for less than 10 years, a decision brought to the national Court by Glaxo.

The overview below summarises the points of view of the three parties (MCA, innovator companies and generic companies) involved in the proceedings:

¹ The ATC code for captopril is C09AA01, classifying it at the third level in the groups of cardiovascular system (C), agents acting in the renin-angiotensin system (C09) and ACE inhibitors, plain (C09A). As the effect of captopril on both the diabetic nephropathy and the myocardial infarction is due to the inhibitory effect of the drug on the angiotensin-converting enzyme (ACE), the ATC classification does not differ for these indications, what invalidates the MCA’s argument.

1. The MCA's Position:

As described above, the British Authority was of the opinion that if an applicant could show that its product is essentially similar to the original product, the abridged procedure according to Article 4.8 (a) (iii) of Directive 65/65 was applicable for all indications, dosage schedules, doses or dosage forms and for all additions or changes hereof whether or not granted during the last 10 years, unless representing a major therapeutic innovation which required a new application according to Annex II to Regulation No 541/95. In this case, a new protection period of 10 years was commenced.

Legal justification:

By extrapolating the variation Regulation (EC) 541/95, the MCA sought for a pragmatic approach to protect the fruits of incremental research and investment of innovative industry, as it was one of the reasons for the implementation of Directive 87/21/EEC as stated in the recitals. On the other hand, by not protecting “minor” changes or additions to an existing authorisation, the MCA thought to prevent pseudo-innovations and unnecessary repetitive clinical and preclinical testing.

Interestingly, the European Commission developed its own policy published in the Notice to Applicant of 1998 [10], which supported the MCA's approach to some extent by stating that new data submitted to support changes representing major new therapeutic innovations should gain an additional 6 to 10-year period of protection. Since these changes were thought to arise mainly in the area of new indications, the level of innovation should be estimated by checking if the change would have been sufficient to justify a centralised authorisation under Part B of Regulation 2309/93 and whether the innovation had been patented. (Noteworthy that 12 years later, with the introduction of the new European pharmaceutical legislation, this point of view was completely inverted by Article 6 (1) of Directive 2004/27/EC [11] which introduces the principle of the global marketing authorisation excluding independent data protection for variations and line extensions (see chapter 2.7))

2. The innovator companies' position:

The innovator companies insisted on their view that the abridged procedure can only be applied if the second applicant can not only show that his product is comparable to the reference product which has been authorized for not less than 10 years, but also that each

therapeutic indication, dose, dosage form or dosage schedule has been authorised for not less than 10 years.

Legal justification:

The research based companies thereby relied on the recitals of Directive 87/21/EEC that innovator companies should not be placed on disadvantage by the definition of the conditions for the exemption of clinical trials for abridged applications. They further drew attention to the fact that in the Notice to Applicants of 1993 [12], the need for the compared products to have the same therapeutic indications was claimed, reflecting the Commission's opinion at that time point. It should be mentioned, that this detail disappeared in the NtA draft document of 1994 [14] without explanation.

The generic companies' position:

The generic companies took the view that the abridged application was applicable for a product essentially similar to an original product which has been authorised for not less than 10 years in respect of any therapeutic indication, dose, dosage form or dosage schedule, irrespective of when the marketing authorisation was changed or a new marketing authorisation was granted.

Legal justification:

Like the research based companies, this party also referred to the recitals of Directive 87/21/EEC, which besides the statement cited by the opposing party claimed that its purpose was to avoid repetitive testing on humans or animals without substantial cause. They further relied on the definition of "essential similarity" noted in the non-binding minutes of the Council of Ministers in December 1986, which says that a product is to be considered essentially similar if

"(i) it has the same qualitative and quantitative composition in terms of active principles, and (ii) the pharmaceutical form is the same and (iii) where necessary, appropriate bioavailability studies have been carried out in accordance with the principles set out in Annex X to Court recommendation...".

In the generic companies' opinion, when applying this definition, the development of new indications was irrelevant for the assessment of essential similarity and therefore not eligible

for a new period of data protection. This definition of the Council was integrated in the current Notice to Applicants of 1998 at the time of the proceedings.

It obviously became clear that the definition of “essential similar” was absolutely critical to the decision on the actual proceedings and the operation of future abridged applications. In essence, two possibilities of interpretation had become apparent:

- a) If “essential similarity was interpreted in a way that focused merely on the active substance of the originator product and not on all characteristics of the product, the first authorisation of the product would have started a single data protection period of six or ten years. The additional presentation and authorisation of new data based on the same compound would not gain further protection and would only benefit from the period unexpired at the date of authorisation.
- b) In contrast, if essential similarity was to be applied to all characteristics of the first product which triggered the need for clinical and/or preclinical data including the active substance, indications, doses etc., a major variation by the originator underlayed by fundamental research would lead to a further protection of six or ten years for the new but not the older data.

2.2.2 The Questions

As the above mentioned cases basically concerned the same issues, the High Court of Justice of UK decided to stay these proceedings and referred the following series of questions to the European Court of Justice relating to the definition of essential similarity and its implication on data protection for new indications or dosage forms, doses and dosage schedules:

- 1) *(a) What is meant by “essential similarity” for the purpose of Article 4.8 (a) (iii) of Council Directive 65/65/EEC (as amended)? In particular, when seeking to establish for that purpose that a medicinal product (product **B**) is essentially similar to a medicinal product which has been authorised within the Community for 6 or 10 years in accordance with the Community provisions in force (product **A**), by reference of which physical or*

other characteristics or attributes of the medicinal product in question should this be determined?

(b) Furthermore, does the competent Authority of a Member State have a margin of discretion in determining the criteria for similarity of product B to product A and if so, to what extent?

2) *May product B be authorised in accordance with Article 4.8(a)(iii) of Directive 65/65/EEC (as amended) in respect of:*

(a) all indications for which product A is currently authorised in the relevant Member State at the date of the application made in relation to product B; or

(b) only those indications for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years; or

(c) only:

(1) those indications for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years; and

(2) those indications for which product A has been authorised for a shorter period, and which did not require an application for the grant of a new marketing authorisation under the provisions of Annex II of Commission Regulation 541/95 or (as the case may be) would not have required such an application had the said regulation been in force at the time the indication in question was added by variation to an existing authorisation; or

(d) some other category of indications, and if so which?

3) *May product B be authorised in accordance with Article 4.8(a)(iii) of Directive 65/65/EEC (as amended) in respect of:*

(a) all dosage forms and/or doses and/or dosage schedules for which product A is currently authorised in the relevant Member State at the date of the application made in relation to product B; or

(b) only those dosage forms and/or doses and/or dosage schedules for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years; or

(c) only:

(1) those dosage forms and/or doses and/or dosage schedules for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years; and

(2) those dosage forms and/or doses and/or dosage schedules for which product A has been authorised for a shorter period, and which did not require an application for the grant of a new marketing authorisation under the provisions of Annex II of Commission Regulation 541/95 or (as the case may be) would not have required such an application had the said regulation been in force at the time the dosage form and/or dose and/or dosage schedule in question was added by variation to an existing authorisation; or

(d) some other category of dosage forms and/or doses and/or dosage schedules, and if so which?

4) Does it make any difference to the answer to Questions 2 and/or 3 whether the original or abridged applications for marketing authorisations were made before 16 March 1995, the date upon which Commission Regulation 541/95 entered into force?

5) In the light of the answers to Questions 1 to 4 above, is Article 4.8(a)(iii) invalid as contrary to the principles of protection of innovation and/or non-discrimination and/or proportionality and/or respect for property?

2.2.3 The Answers

The first question:

The European Court of Justice began its answer by underlining that the abridged application pointed out in Article 4.8(a) cannot be interpreted in a way that softens the law's provision to

ensure the conditions of safety and efficacy which must be met by a medicinal product. Therefore, Article 4.8(iii) sets out the obligation for the applicant to show that his product is that similar to the first product that they do not differ significantly in respect of safety and efficacy.

For the definition of “essentially similar”, the Court followed the definition provided by the Council of Ministers in its minutes of meeting of December 1986, where the three main criteria were given:

Product A and product B are only essentially similar, if they satisfy three main criteria, namely that they:

- have the same qualitative and quantitative composition in terms of active principles;
- have the same pharmaceutical form and
- (where necessary) bioequivalence of the two products has been established by appropriate bioavailability studies.

The Court also referred to the fact that this concept has been incorporated in the Notice to Applicants, which by definition is a guideline and therefore not binding, but that according to the Annex to Council Directive 75/318/EEC, the information provided for an abridged application have to take account of those rules [14].

As regards the criterion of bioavailability, the Court cited the CPMP Guidelines on Investigation of Bioavailability and Bioequivalence (87/176/EEC) [15]. This guidance states that products are bioequivalent

“if they are pharmaceutical equivalents or alternatives and if their bioavailabilities (rate and extent) after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same”.

Interestingly, in citing the guideline, the Court did not further comment on the term pharmaceutical alternatives, which are defined by the same guideline as products which contain the same therapeutic moiety but differ in chemical form (e.g. salt or ester) or in the dosage, form or strength. All of these issues will be addressed in subsequent cases.

Nevertheless, an exemption from this setting was made if the product in question differed significantly from its comparator in the light of efficacy or safety, which might for example

be related to its excipients. In this case, the Court declared that although meeting the three criteria defined above, the medicinal product cannot be regarded as essentially similar.

The Court secluded its answer by deciding that the competent Authority has no margin of discretion in determining the criteria to be applied and must not disregard the criteria now defined by the Court, thereby harmonising the diverse Authority handling of the issue by national authorities and Courts.

The second and third question:

In the answer to the second and third question, the Court declared a very clear position. The Court pointed out that having the same therapeutic indications and/or dosage forms, doses and dosage schedules is not one of the criteria which, according to its judgment, must be satisfied in order that two medicinal products may be regarded as essentially similar. Therefore, the Court deduced that a generic product which has been shown to be essentially similar to a first product authorized in the Community for not less than 6 or 10 years may be authorised in respect to all indications and/or dosage forms, doses and dosage schedules already granted for the original product, including those authorised for less than 6 or 10 years.

Additionally, the Court rejects the proposal of the Commission of granting new protection periods for therapeutic indications representing a major therapeutic innovation by means of categorisation according to Annex B of Regulation 2309/93 or the patent registration of the indication as already discussed above. The Court stated again that this proceeding would be contrary to the specifications set by Directive 65/65/EEC and the definition of essential similarity. Furthermore, the Court criticized the imprecise concept proposed for the classification of therapeutic indications and which would for this reason undermine the principle of legal certainty.

In the same way, the Court disagreed with the MCA's procedure to grant a new period of protection for new indications categorized as major changes and demanding a new application according to Annex II to Regulation No 541/95. The Court referred to the purpose of this Regulation to harmonise administrative practices applicable to changes of marketing authorisation and concluded that this proceeding is not adequate.

Finally, the Court pointed out that it is a matter of Community legislation rather than jurisdiction to create a legal basis for the protection of innovative research as concerned in the actual case and with this passed the ball back to the Commission to decide on the creation of

data protection periods for innovative indications, which has been realized 7 years later with the implementation of the new Pharmaceutical legislation.

Interestingly to note is the change of the Commission's position on the protection of new indications, which developed from full protection (NtA 1993) over protection for significant innovations (NtA 1998) to no protection (NtA 2000) and back to protection of significant innovations (2004/27/EC).

The fourth question:

As Regulation No. 541/95 had no relevance to the application of Article 4.8(a)(iii) of Directive 65/65/EC according to the current ruling, the Court decided that the date on which this regulation entered into force had no significance for the case.

The fifth question:

In its answer to the fifth question, the Court rejected the issues of infringement of the principles of protection of innovation, non-discrimination, proportionality and respect for property. The main arguments for this position were that the abridged procedure does not give an unjustified advantage to the second applicant by exempting it from the need to provide preclinical and clinical data, but avoids the repetition of tests on humans or animals unless absolutely necessary, which in turn suits the primary purpose of any rule concerning the production and distribution of medicinal products, namely the protection of public health. Since the first applicant has no other possibility as to prove the safety and efficacy of its product by testings, he is not in the same situation as the second applicant, who can rely on the data of the former. Nevertheless, the Court emphasized that the property of research based companies is appropriately protected by the 6 or 10 years period of data protection.

Although providing a clear basis and legislative guidance for a set of fundamental questions, many issues for example protection of line extensions or different salts or esters of the active moiety were left open and therefore designated to further juridical investigation as shown in the next chapter.

2.3 Case C-106/01 – Essential similarity revisited [16]

2.3.1 The Dispute

In April 2001, nearly four years after *Generics*, the second trend-setting case was decided by the European Court of Justice dealing with essential similarity and the abridged procedure. The dispute in this case was about the UK Medicines Control Agency's (MCA) approval of a marketing authorization for the medicinal product SangCya by SangStat UK Ltd ('SangStat') via the abridged procedure using the product Sandimmun by Novartis Pharmaceutical Ltd ('Novartis') as a reference product.

The Novartis product Sandimmun is an immuno-suppressant containing the active ingredient cyclosporin and was first authorized within the Community in 1983. Its first-line indication was the use for the prevention of organ rejection in transplantation surgery. The product was characterized by a narrow therapeutic window and therefore required a tightly controlled dose range to ensure clinical efficacy with an acceptable safety profile. Therefore, bioavailability was of high importance to minimize the risk of organ rejection in case of too low cyclosporin blood levels on the one hand and impairment of kidney immune system function on the other hand.

To overcome existing deficiencies of Sandimmun in the light of absorption and administration, Novartis developed the subsequent product Neoral. The pharmaceutical form of both products differed slightly: although both were administered orally as a solution to the patient, Sandimmun formed a macroemulsion in an aqueous solution, whereas Neoral formed a microemulsion, which differs in the size of the dispersed cyclosporin droplets. As a result, Neoral showed supra-bioavailability to Sandimmun, because of faster absorption and higher resistance to concomitant food intake. The authorization for Neoral by the MCA in 1995 was granted following a hybrid abridged procedure pursuant to Article 4.8(a)(i) of Directive 65/65 with the consent of Novartis itself as the marketing authorization holder of Sandimmun and application of the proviso for additional pre-clinical and clinical bridging data specific to Neoral.

The third product involved in the proceeding was the already mentioned product SangCya by SangStat, which was approved by the MCA in 1999. Although containing cyclosporin as the active ingredient and being administered orally as a solution, too, SangCya differed from both Sandimmun and Neoral in forming a nanodispersion when mixed in an aqueous solution. As a

consequence, SangCya was not bioequivalent to both Novartis products because of the variation in the products` bioavailability. Accordingly, SangStat provided with its application data to show the supra-bioavailability of SangCya to Sandimmun.

Nevertheless, SangStat claimed essential similarity of both products and used the abridged procedure relying on Article 4.8(a)(iii) of Directive 65/65 referring to Sandimmun as the reference product, which had at this time point been authorized for more than 10 years. For the purpose of granting marketing authorization for SangCya, the MCA also relied on data submitted by Novartis in the context of its Neoral application and approved the product in 1999.

Novartis subsequently challenged the MCA`s decision on the basis of the following three arguments:

1. Novartis claimed that the MCA was not entitled to refer in the context of the abridged procedure to its data submitted for Neoral because of the fact that the product was authorized for less than 10 years at the time of submission of the SangCya application.
2. Since SangCya was not bioequivalent to Neoral, Novartis considered the MCA`s finding of SangCya being essential similar to Sandimmun illegal together with the consequential excuse of SangStat from showing the safety of its product.
3. Finally, Novartis argued that the decision infringed the principle of non-discrimination because the assessment of Neoral and SangCya were not treated equally in terms of required data without an objective justification.

2.3.2 The Questions

The Court of Appeal of England and Wales decided to refer the case to the European Court of Justice for preliminary ruling and asked for clarification of six questions:

- 1) In considering a marketing authorisation for a new product (C) under Article 4.8(a)(iii) of Directive 65/65, referencing a product (A) authorised more than 6/10 years ago, is a national competent Authority ever entitled to cross-refer, without consent, to data submitted in support of a product (B) which was authorised within the last 6/10 years?*

2) *If so, may such cross-reference be made in circumstances where:*

(a) product B was authorised under the Article 4.8(a) hybrid abridged procedure, referencing product A; and

(b) the data to which reference is made consists of clinical trials which the national competent Authority indicated would be necessary if the marketing authorisation was to be granted and which were submitted in order to demonstrate that product B, though suprabioavailable to product A when administered in the same dose, is safe?

3) *(a) Does the final subparagraph of Article 4.8(a) of Directive 65/65 ("the proviso") apply only to applications made under Article 4.8(a)(iii) or to applications made under Article 4.8(a)(i) also?*

(b) Is essential similarity a prerequisite for the use of the proviso?

4) *Can products ever be essentially similar for the purposes of Article 4.8(a)(i) and (iii) of Directive 65/65 when they are not bioequivalent, and if so in what circumstances?*

5) *What is the meaning of the term pharmaceutical form, as used by the Court in its judgment in Case C-368/96 Generics? In particular, do two products have the same pharmaceutical form when they are administered to the patient in the form of a solution diluted to a macroemulsion, microemulsion and nanodispersion respectively?*

6) *Is it consistent with the general principle of non-discrimination for a national competent Authority, faced with hybrid applications for marketing authorisations under Article 4.8(a) of Directive 65/65 referencing product A for two products, neither of which is bioequivalent to product A:*

(i) to indicate that it is necessary for a marketing authorisation to be granted for product B to be supported by full clinical data of the type required by Part 4(F) of the Annex to Directive 75/318/EEC; but

(ii) having considered the data filed in support of product B, to grant a marketing authorisation for product C if that application is supported by trials not meeting the requirements of Part 4(F) of the Annex to Directive 75/318/EEC?

2.3.3 The Answers

The fourth question:

The Court decided to start its answer with the fourth question dealing with the essential similarity issue. Referring to the definition provided in the *Generics* case, the Court cited again the conditions for essential similarity. Since bioequivalence is one of the three explicit criteria, the Court held that products can not be regarded as essentially similar for the purpose of an application pursuant to Article 4.8(a)(i) or (iii) of Directive 65/65, when they are not bioequivalent and stayed clearly in line with its earlier ruling.

The fifth question:

The Court continued with the fifth question seeking for a definition of the term “pharmaceutical form” and referred in its answer to the definition given by the Council of Europe in the list of reference terms of the European Pharmacopoeia. In this text, the pharmaceutical form is defined as the combination of the form in which a pharmaceutical product is presented by the manufacturer and the form in which it is administered, including the physical form. In the case under issue, the Court interpreted that Sandimmun, Neoral and SangCya, although showing differences in the form of administration as they form a macroemulsion, a microemulsion and a nanodispersion, respectively, in aqueous solution, are to be treated as having the same pharmaceutical form, provided that the differences in the form of administration are not significant in scientific terms.

Unfortunately, the Court did not provide further argumentation for its decision on this question and also did not comment what is exactly meant by “significant in scientific term”. Furthermore, there was no comment on the argument of Novartis holding that differences between products resulting from their respective formation of dispersions or emulsions may affect their comparative bioavailability and may therefore impact on their safety and efficacy, a fact that would make it comprehensible if these presentations would be considered as different pharmaceutical forms. At least the Advocate General Francis Jacobs commented on

this statement and argued that since bioequivalence is in any event an independent requirement of essential similarity, he felt that the interpretation of pharmaceutical form need not to be influenced by a concern to ensure bioequivalence. To some extent, the opinion of the Advocate General is not easy to follow having in mind that for example solid oral forms for immediate release are differed from solid oral forms for prolonged release, which is certainly due to their differing pharmacokinetic profile and bioavailability. Nevertheless, a sound definition of the term significant in scientific terms would have made it easier to follow the Courts ruling at this point.

The third question:

The Court's answer to the third question relating to the use of the proviso was very straight forward and mainly reflected the opinion forwarded by SangStat and the UK Authority. First, the Court declared that the proviso was applicable to applications provided with (Article 4.8(a)(i)) and without (Article 4.8(a)(iii)) consent of the first marketing authorisation holder, since the underlying purpose to avoid repeated testing on humans and animals is a policy that applies to both procedures. Needless to say that this ruling was in the sense of SangStat as well as of Novartis, because both the originator and the generic company applied for their authorisations relying on the proviso but using Article 4.8(a)(i) and Article 4.8(a)(iii), respectively.

In the second part of the proviso issue lighting the question if essential similarity is a strict prerequisite for the use of the proviso, the Court differentiated two scenarios by separating the conditions provided in the proviso:

a) The second product differs from the first only in terms of its therapeutic indications.

The Court argued essential similarity is the main condition for the application of the abridged procedure and that under the proviso, the first and the second product may differ in terms of their therapeutic indications. Since the therapeutic indication is not a criterion for essential similarity, the prerequisite of meeting this criterion as a basis for the application of the procedure remains unaffected.

b) The second product has to be administered by different routes or in different doses than the first one.

In this case, the Court agreed with SangStat and the UK Authority that a second product differing in its administration routes or dosing is likely to have a different bioavailability and therefore to be not bioequivalent to the reference product. Furthermore, a change to the dose of a product might constitute a change in the quantitative composition and therefore preclude essential similarity. Accordingly, if essential similarity would be a prerequisite for the application of the proviso, this provision could not be applied for many products differing in dosing or routes of application from the first product, although explicitly mentioned in the proviso.

The Court finally pointed at the interpretation of the proviso published in the Notice to Applicants in the version of 1993, where it was stated that the proviso could be applied where the generic product did not strictly satisfy the criteria of essential similarity. Noteworthy, this remark did not appear again in later version of the Notice to Applicants, but there were also no contradictory statements published.

The first and second question:

The answers to questions one and two, which should be read in conjunction, are the most controversially discussed and perhaps the most difficult to understand, last but not least caused by the fact that it did not become clear from the judgement what kind of bridging data was submitted by Novartis and SangStat for their respective hybrid application.

In summary, the Court was asked to decide on whether a competent Authority when considering a marketing authorisation for a new product C (in this case SangCya) in an abridged application pursuant to Article 4.8(a)(iii) referencing product A (Sandimmun) authorised for more than 6 or 10 years ago, could cross-refer to data submitted for the application of product B (Neoral) which was authorised under the proviso for less than 6 or 10 year and which show that product B, though suprabioavailable to product A is safe.

The Court began its answer in consistency with the ruling of *Generics*, stating that neither data submitted for a new therapeutic indication nor a new route of administration or dose can be accorded a new period of protection. Leaving the ruling of *Generics* untouched, which claims the right to refer to data for all indications, routes and doses if the second product is essentially similar to the first one, the Court expanded this right to products which were not essentially similar to the reference product in respect of its routes and doses. In accordance with the answer to the third question, the Court explained that if cross-reference to the data

submitted for product B was only permitted if product B and A were essentially similar, this would largely restrict cross-reference to data submitted to support the application for a new indication, since products which are to be administered by different routes or doses are likely to differ from the first product A in their bioavailability and therefore will not be bioequivalent. The Court made clear that product B is not to be considered a new and “independent” product, but that under the light of the proviso such a product is a development of the original product and with the afore said not eligible to an independent period of data protection, a rule that equally applies for products authorized as line extensions following a complete application according to Article 8.3(i).

Although being clearly stated and comprehensible, the answer to the first question was not sufficient in the case at hand, since the difference in bioequivalence between Neoral and Sandimmun was not due to the circumstances set forth in the proviso. Although Neoral was not bioequivalent to Sandimmun, it was not approved for a new route of administration or dose. To approach this problem, the Court extrapolated from the fact that it is possible to refer to data of a line extension which is not bioequivalent to the original product due to differences in the route of administration or dosing (which is in accordance with the answer to question three), that a lack of bioequivalence for reasons unrelated to a difference in the route of administration or dose does not prevent a third party from relying on data from that line extension.

At a first glance, this decision of the Court seems to be quite spectacular because it seems to annihilate the ruling of *Generics* and to water down the requirement of essential similarity for the abridged application which were set to protect public health and to prevent discrimination of originator companies` rights. On closer reflection, it can be interpreted that the Court`s ruling uncovers an inconsistency in the wording of Article 4.8(a)(i) and (iii) which discriminates the cross-reference to products having characteristics which indeed do not fit the conditions of the proviso but at the same time lead to the same effect in respect to the comparability to the original product, namely not being essentially similar. Coming back to the fact that not only Neoral is not bioequivalent to Sandimmun but that SangCya is neither bioequivalent to Neoral nor Sandimmun, one has to assume that the bridging data submitted by Novartis for the application of Neoral must have been of a nature that rendered it transferable to SangCya giving evidence for the safety of this third product. Apart from this, the ruling of the Court did not preclude the competent Authority from demanding additional

data from the generic applicant in case the bridging data for the line extension were not convincing enough to prove the safety of the third product.

In essence, the Court granted the same right to SangStat and to Novartis, who both used the hybrid abridged procedure for products which could not be considered essentially similar to Sandimmun due to their suprabioavailability.

The sixth question:

Having answered the first five questions, the last question dealing with the non-discrimination issue was answered as a logical continuation according to the developed line of argument. The Court underlined that the situation for the authorisation application for Neoral differed from that of SangCya in so far as at the time the submission for the latter was made, Neoral was already authorised and proven to be safe and efficacious in a way that the data thereof could be used to support the application for SangCya. Therefore, the Court decided that the procedure in question did not infringe the principle of non-discrimination.

With this ruling, the Court clearly opened the door for generic companies to rely on data for any kind of line extensions of original products, a tendency which will be consolidated in case C-36/03 described below.

2.4 Case C-36/03 – a logical continuation of the Novartis case [17]

As mentioned above, case C-36/03 appears as the consolidation of the preceding Novartis case. The case concerned three medicinal products all containing the active substance fluoxetine.

2.4.1 The Dispute

In 1988, Eli Lilly & Co. Ltd ('Eli Lilly') received a marketing authorisation for the product Prozac capsules in the UK. The second product, Prozac liquid, was authorized in the UK in 1992 following an application made by Eli Lilly under the hybrid abridged procedure. Eli Lilly provided for this purpose additional data to show that the products were bioequivalent despite their different pharmaceutical form, which excluded them from being essentially similar.

In 1999, Approved Prescription Services Ltd ('APS') sought for authorisation of the third product, Fluoxetine liquid 20 mg/5 ml and thereby sought to rely on the abridged procedure under Article 10(1)(a)(iii) of Directive 2001/83 (the equivalent to Article 4.8(a)(iii) of Directive 65/65) in the codified text). APS justified this strategy by stating that its product was essentially similar to Prozac liquid and provided additional data on this and by stating that the original product was Prozac capsules which was at that time authorised for more than 10 years in the Community.

The UK Authority MHRA rejected the application by arguing that APS could not refer to the data provided by Eli Lilly for Prozac liquid because this product was authorised for less than 10 years and if choosing Prozac capsules as the reference product, the company must therefore provide additional data proving that the generic product was bioequivalent to the first. In consequence, APS brought an application to the High Court of Appeal, which decided to refer the following question to the European Court of Justice:

2.4.2 The Questions and Answers

Can an application for a marketing authorisation for a medicinal Product C validly be made under the first paragraph of Article 10(1)(a)(iii) of Directive 2001/83, where the application seeks to demonstrate that Product C is essentially similar to another product, Product B, in circumstances where:

- *Product B is related to an original medicinal Product A, in that Product B has been authorised as a “line extension” of Product A, but has a different pharmaceutical form from Product A or is otherwise not “essentially similar” to Product A within the meaning of Article 10(1)(a)(iii); and*
- *Product A has been authorised for marketing in the Community for more than the six/ten year period stipulated in Article 10(1)(a)(iii); and*
- *Product B has been authorised for marketing for less than the six/ten year period stipulated in Article 10(1)(a)(iii)?*

The ruling of the Court on this case is very straightforward and in line with the Novartis decision. The Court held that if an applicant, according to the ruling in the Novartis case, is entitled to make reference to data relating to a product B, which differs from the reference product A only in its bioavailability, even though the route of administration and dose remains

unchanged, the same must apply to products which differ from the original product in having a different pharmaceutical form. This was concluded by the Court from the assumption that a change in the route of administration generally implies a new pharmaceutical form which makes the issue comparable to that in the Novartis Case.

The Court substantiated its argumentation by referring to the Notice of Applicants in the version of 2001, where it is expressively stated that

“the dossier of a new strength, new pharmaceutical form, new indication (called deliberately ‘line extensions’ see section 5.2) of an existing medicinal product from the same marketing authorisation holder based on a complete dossier is also considered as a complete dossier. An essentially similar product (informed consent or generic) can refer to the dossier of the line extension of the original medicinal product. Therefore, a line extension for a generic medicinal product can be applied for by reference to the line extension of the original medicinal product.” [18].

Additionally, according to the Novartis Case, no new period of data protection applies to a line extension of a reference product. Therefore, reference to the line extension is possible even if it has been authorised in the Community for less than 6 or 10 years.

The Court ends with the addition that although the decision in the Novartis Case made reference to the provisions laid down in the proviso, the generic applicant must not rely on the provision when making its application.

2.5 Case C-74/03 – Different salts of the active substance can be similar [19]

2.5.1 The Dispute

The latest case of the European Court of Justice dealing with the definition and interpretation of essential similarity was decided in January 2005. This proceeding concerns the challenge of the granting of a marketing authorisation for the paroxetine products of the generic companies Synthon BV and Genthon BV (‘Synthon’ and ‘Genthon’) by the originator company SmithKline Beecham plc (‘SmithKline Beecham’). In 1993, SmithKline Beecham obtained an authorisation for the product “Seroxat”, which contains as the active substance paroxetine hydrochloride hemi-hydrate. In 1999, the companies Synthon and Genthon applied for a marketing authorisation following the abridged procedure in Denmark, a member state which provides a 6-year protection period for innovative products. Synthon and Genthon cited

Seroxat as the reference product as their product also contains paroxetine as the active principle, although in the form of a different salt, namely paroxetine mesylate. Aware of this apparent discrepancy, Synthon and Genthon submitted data resulting from selected pharmacological and toxicological tests on animals to show that the two products were essentially similar despite containing different salts of the active substance. The Danish Authority subsequently requested even further information and after having evaluated the supplied data concluded that there were virtually no differences between the two salts as far as toxicity concerned. As the bioavailability of both forms was also comparable, the Danish Authority granted marketing authorisations for the Synthon/Genthon product.

For the purpose of their challenge, SmithKline Beecham argued that Seroxat and the Synthon/Genthon product were not the same because they contained (though related) different active substances. According to SmithKline Beecham's argumentation, this was confirmed by the mere fact that additional pharmacological and toxicological data were necessary to demonstrate essential similarity. As a second point, the company mentioned that in the context of the abridged procedure, submission of further data of pre-clinical or clinical tests was permitted only in situations where the proviso applied, namely where the second product was intended for a different therapeutic indication or was to be administered by different routes or in different doses. They further pointed at the importance of the distinction between the abridged procedure under Article 4.8(a)(iii) and the hybrid abridged procedure pursuant to the proviso. In their opinion, this difference would be blurred down if the definition of essential similarity adopted by the Court in the *Generics Case* were to be relaxed and the routine submission of additional data were allowed in a wider range of circumstances than those included within the proviso.

Proceeding with their line of argument, the company claimed that the definition of essential similarity provided in *Generics* should be understood in a way that if the three stated criteria are met, it safely can be assumed that the first and second product will have the same safety and efficacy profile, which at the same time represented the additional criterion for essential similarity. However, this condition should be employed only as an additional safeguard against the risk that a change in the excipients used might render a second product less safe or efficacious.

If two active substances containing different salts of the same therapeutic principle would be considered the same, the criterion "of having the same qualitative and quantitative

composition in terms of active principle” could no longer be considered as an appropriate measure for the similarity in respect of safety and efficacy. The substitution of a salt by another could change the absorption and bioavailability of the active ingredients and with it their therapeutic efficacy, toxic potential or stability leading to converse properties.

Therefore, the applicant would routinely be considered to supply additional data proving the comparability of the safety and efficacy profile of both products despite of the changed salts. As a consequence, “having the same qualitative and quantitative composition in terms of active principle” would no longer be an independent criterion but would be substituted by the safety/efficacy aspect.

2.5.2 The Questions and Answers

The points at issue were resumed in two questions which were referred to the ECJ (the original order of the questions was the other way around, but due to the line of argument, the Court answered the second question first):

1) The second question: Can the abridged application procedure be used when an applicant, on its own initiative or at the request of national health authorities, submits additional documentation in the form of certain pharmacological or toxicological test or clinical trials with a view to demonstrating that the product is “essential similar” to the reference product?

The Court’s answer to this question was very short and precise. The Court began with the remark that according to Article 4.8(a) of Directive 65/65, the applicant is not required to submit pre-clinical or clinical data if he can demonstrate that his product is essential similar to the reference product. To demonstrate this, the applicant may have to supply additional data.

The Court also pointed out that the additional data to be provided in the above mentioned case pursue a different aim than that demanded in the context of the proviso. Whereas the former aims at proving the similarity of two products, the latter are designed to compensate for the lack of essential similarity. Moreover, there is no clause in the proviso which restricts the submission of additional data to applications which are handled pursuant to that provision.

Therefore, the Court concluded that in support of an abridged application under Article 4.8(a)(iii), the applicant may of its own accord or at the request of the competent Authority

supply additional results of pre-clinical or clinical testing in order to demonstrate that his product is essentially similar to the reference product.

2) *The first question: Is it compatible with Article 4.8(a)(iii) of Directive 65/65 for a product to be authorised under the abridged application procedure when a salt of the active substance in the product is changed from the one used in the reference product?*

In its answer to the first question, the Court obviously supported the view of the generic companies. The Court agreed with the Danish Government and Synthon's/Gentho's view that the criterion defined in *Generics* does not imply that there must be an exact molecular match between the active substances and that it is more appropriate to base the evaluation of similarity on therapeutic action than on the precise molecular structure of the active substances. The Court pointed out that the term "active principle" was not defined in the *Generics* case, but is apparent to be used for both the therapeutical active part of an active substance on the one hand and the active substance itself on the other hand. Additionally, neither the wording in Article 4.8(a)(iii) of Directive 65/65 nor the definition given by the Court in *Generics* excluded the possibility that two products containing different salts of the same active moiety might be essentially similar.

The Court compared the risk of affecting the safety or efficacy of the product by changing the form of salt of the active substance to the risk which might result from a change of an excipient of a medicinal product and therefore not considered it sufficient to imply that the products are not essentially similar.

The claim that the definition of essential similarity should be applied strictly to ensure a fair balance between the interests of innovator and generic companies was invalidated by the Court by pointing out that the originators are protected by the 6 or 10 year period of data exclusivity provided. Furthermore, the Court clearly stated that the requirement of essential similarity for the abridged procedure has in the first place been designed to protect public health and that a specific objective of the abridged procedure is to allow economic expenditure of time and cost to produce appropriate preclinical and clinical data and especially to avoid unnecessary and repetitive testing on humans and animals.

The Court also referred to the Notice to Applicants in its version of 1998 which was in force when Synthon and Gentho applied for the marketing authorisation. In this issue, explicit advice is given on additional data to be provided when applying for a marketing authorisation

under the abridged procedure, if different salt or ester complex or derivative with the same therapeutic moiety are contained in the product, namely “evidence that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could change the safety/efficacy profile”, and indicating that otherwise it has to be considered as a new substance.

Noteworthy, in its opinion to the case, the Advocate General Francis Jacobs also cites the NtA version of 2001, which was indeed not in force at the time of the Synthon/Genthon application, but which nevertheless reflects the current opinion and understanding of the commission concerning the legal basis and practice applied for marketing authorisation procedures in the European Union. In this issue, a new active substance is defined as “ an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regard to safety and efficacy from that chemical substance previously authorised.

At the end of its opinion, the Court did not even bother to describe in detail the reasons for the rejection of three further arguments of SmithKline but only referred to the opinion of the Advocate General. The three arguments and the reasons for rejection are outlined below:

- *The innovator company referred to the definition of “qualitative composition” of a medicinal product given in the Annex to Directive 75/318, implying that the active ingredient should be understood, in the case of salts, to include both the therapeutic moiety and the appended portion of the molecule, and should be identified as such.*

The Advocate General made clear that in his opinion, this definition is not applicable for the interpretation of the criteria of essential similarity specified by the Court in the *Generics* case. He counter-argued that this definition was set out for giving advice on the particulars and documents which must accompany applications for marketing authorisation and that in that context, it makes sense that the qualitative composition of the active ingredient should be exhaustively described.

- *SmithKline Beecham made reference to Commission Regulation (EC) No 541/95 concerning the examination of variations..., Annex II of which requires that a new marketing authorisation be applied in the event of “changes to the active substance(s)”*

which, according to that Annex, includes “replacement of the active substance(s) by a different salt... (with the same therapeutic moiety)”.

In its comment to this argument, the Advocate General immediately brought to mind that the Court specifically ruled in *Generics* that Annex II to Regulation No 541/95 is of no relevance to the application of Article 4.8(a)(iii) of the Directive. Additionally, he pointed out that many of the types of changes identified in Annex II would fall within the hybrid abridged procedure provided for in the proviso to Article 4.8(a) (i.e. changes to the indication, changes to strength, pharmaceutical form and route of administration).

- *In the last argument, the research based company pointed at the definitions contained in Commission Regulation (EC) No 847/2000 laying down the provisions for the implementation of the criteria for the designation of a medicinal product as an orphan medicinal product and definitions of the concepts “similar medicinal products”:*

A similar active substance is defined as ‘an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism’. It is defined to include ‘isomers, mixture of isomers, complexes, esters, salts and non-covalent derivatives of the original active substance, or an active substance that differs from the original active substance only with respect to minor changes in the molecular structure, such as a structural analogue’ [20]

The Advocate General explained that Regulation No 847/2000 was not relevant for the interpretation of Article 4.8(a)(iii) of the Directive 65/65. He straightened out that two products containing different salts of the same active moiety can never be considered identical, but that the current question aimed on the decision if they nevertheless can have the same qualitative and quantitative composition in terms of active principles.

Taken all together, the Court decided on the first question that “Article 4.8(a)(iii) of Directive 65/65 must be interpreted as not preventing an application for a marketing authorisation in respect of a medicinal product from being handled under the abridged procedure under that provision where that product contains the same therapeutic moiety as the reference product but combined with another salt.”

2.6 Generic application beyond ECJ – the summary

As already mentioned above, the European Court's jurisdiction gave a tremendous boost to the generic industry and opened the door for second applications to a wider range of products without the obligation to submit additional data, thereby speeding up time to market and avoiding additional costs for the generation of data.

The following table summarizes the essential findings by the Court which in general line reflect the current practice in authorizing generic medicinal products in the European Union and which also found their way into the new pharmaceutical legislation presented with the Review 2004.

Finding of the European Court of Justice	Case reference
Essential similarity is defined as <ul style="list-style-type: none"> - having the same qualitative and quantitative composition in terms of active principles; - having the same pharmaceutical form and - being bioequivalent to the reference product. 	<i>Generics C-368/96</i>
Different salts of the same active moiety are to be considered the same.	C-74/03
New therapeutic indications, doses or routes of administration do not trigger a new period of data protection for this so called line extensions which can therefore be used as reference product even if authorised less than 6 or 10 years in the Community, as long as the original product is authorised longer than that critical period.	<i>Generics C-368/96</i> <i>Novartis C-106/01</i>

<p>Essential similarity is not a basic prerequisite for hybrid abridged applications, which is excluded by the provisions laid down in the proviso.</p> <p>If the generic product is for any reason not essentially similar to the original product, additional data must be provided proving the efficacy and/or safety of the product. This also applies to abridged applications not under the provision of the proviso.</p>	<p>Novartis C-106/01 C-36/03</p>
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2.7 The new pharmaceutical legislation with the Review 2004 and its implications for generic drug application

In May and November 2004, the European Commission published the new pharmaceutical legislation in the Official Journal of the European Union with the Regulation 726/2004 replacing Regulation 2309/93 on centralized marketing authorisation procedures [21] and Directive 2004/27 amending the Community Code for human medicinal products. The reason for the pharmaceutical review can be found in the text of the old legislation.

As established in Council Regulation 2309/93: “within six years of the entry into force of this Regulation, the Commission shall publish a general report on the experience acquired as a result of the operation of the procedures laid down in this Regulation”. The Commission has taken this opportunity to review the entire regulation of pharmaceutical products for the following main purposes:

- to evaluate the results achieved by the creation of a single market for the medicinal products;
- to evaluate the results of the Centralised Procedure and of the European Medicines Evaluation Agency in order to simplify the registration procedures for medicinal products and favour competitiveness of the pharmaceutical industry;
- to guarantee a high level of public health and to increase transparency for a better access to information for patients;
- to prepare the EU enlargement.

For the sake of completeness it should be added that in addition, Directive 2004/28 amending the Community Code for veterinary products and Directive 2004/24 on herbal medicinal products were also published [22] [23].

As shown on the pages above, the rules on regulatory data protection applicable for the generic authorization procedure have undergone a long process of interpretation and legal approximation. In its decisions on the various cases concerning essential similarity and abridged application, the European Court of Justice developed a view which paralleled the opinion developed by the Commission and published in the Notice to Applicants over the years.

Focusing on data protection issues, many of the new concepts introduced by the new legislation have already been applied by the national Authorities which thereby relied on the ECJ law cases and the Commission's Notice to Applicants. Thus, the new legislation provides a clearer legal basis. Furthermore, in addition to simply reflecting case law evolution, new elements have been introduced which undoubtedly give further boost to the generic industry by removing hurdles like for example patent infringement by conducting tests and trials before patent expiry.

The table below provides an overview of the most important renewals in the new legislation which are connected to data protection and generic drug application.

New legislation	Comment
<p><i>First subparagraph of Article 10(1) of Directive 2004/27:</i></p> <p>By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the</p>	<p>This new article providing the legal basis for generic applications introduces for the first time the term “generic”, which replaces the phrase “essential similar”. In addition, it introduces a new period of data protection for original products which will be 8 years instead of 6 or 10 years according to the previous Directive. This means that 8 years after the authorisation of a reference product has been granted, the second applicant is allowed to file its application.</p> <p>Furthermore, the new legislation deliberates</p>

Community.	the reference product from the condition to be authorised at the time of the second application, but allows for a generic application even if the marketing authorisation for the reference product has been withdrawn or expired.
<p><i>Second subparagraph of Article 10(1) of Directive 2004/27:</i></p> <p>A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.</p>	<p>This subparagraph introduces a new period of market exclusivity for the reference product. Although the second applicant is allowed to file his application 8 years after the initial authorisation of the reference product, he is not allowed to market his product even if authorised before the period of marketing exclusivity has expired. With this new provision, the generic companies gain a substantial advantage in respect of time to market. It additionally reflects the fact that the administrative process of filing and reviewing applications as well as the granting of marketing authorisations does not implicate an infringement of patent rights.</p>
<p><i>Third subparagraph of Article 10(1) of Directive 2004/27:</i></p> <p>The first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent Authority of</p>	<p>This subparagraph not only enables abridged applications in member states where the medicinal product is not authorised (what is not possible according to the current legislation), but also provides the legal basis for generic applications for the centralized procedure according to the Annex of Regulation 726/2004 (e.g. biotechnological products), which refer to a medicinal product that has been authorized according to the ex-concertation procedure and the documentation</p>

<p>the Member State in which the application is submitted, the competent Authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.</p>	<p>of which is therefore accessible to the CHMP for the review process.</p>
<p><i>Fourth subparagraph of Article 10(1) of Directive 2004/27:</i></p> <p>The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.</p>	<p>This provision is also newly introduced in the legislation and represents an incentive for the innovative company for further research and development on already authorised products and reflects the apprehension that the restrictions in data exclusivity and the growing influence of generic companies in the pharmaceutical market and prize politics may restrain innovators from further investments in authorised products.</p>
<p><i>Article 10(2)(b) Directive 2004/27:</i></p> <p>“Generic medicinal product” shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be</p>	<p>This part of Article 10 unites a whole bunch of definitions and decisions of the European Court which has been described in the four law cases above and which also reflect the Commission’s opinion as published in the current version of the <i>Notice to Applicants</i>.</p> <p>Although providing a clearer legal basic for the generic application, the new provisions might nevertheless give reason to further legal action. As for example no definition for a “significant difference” in the context of safety and efficacy properties of the second</p>

<p>considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.</p>	<p>product is provided, this wording is likely to be tested in the Courts.</p>
<p><i>Article 10(3) Directive 2004/27:</i> In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.</p>	<p>With this text, the proviso in Article 10(1)(a)(iii) of the current version of Directive 2001/83 is replaced and the conditions for the submission of bridging data by the second applicant are given. If this list can be considered to be exhaustive will be proven in the future with its broad application.</p>
<p><i>Article 10(4) Directive 2004/27:</i> Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition</p>	<p>For the first time, the possibility to submit applications for “biosimilar” products will be expressly given with implementation of the new legislation in November 2005. Although</p>

<p>of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the Annex and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.</p>	<p>according to the European Commission, the legislative basis for applications for biosimilars is given with Article 10(1)(a)(iii) in conjunction with Annex I, Part II section 4 of Directive 2001/83 (Nicolas Rosignol, 3rd EGA Symposium on Biogenerics, 26.-27. May 2005, London), the new legislation will introduce an explicit basis for this kind of application. As the amount of data to be provided has to be decided on a case by case basis and detailed guidance is not available to date, it can be considered that new law cases will arise from these issues.</p>
<p><i>Article 10(6) of Directive 2004/27:</i> Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.</p>	<p>The issue of patent infringement by conduction of tests and trials during the patent life is at date a considerable hurdle for generic companies. As the legal practice depends in this case on national patent law, some countries have expressly considered that such activities lead to patent infringements whereas others do not. With the introduction of this so-called Bolar-clause, the issue is regulated uniformly in the Community and has to be implemented in national patent laws.</p>
<p><i>Article 6(1) second subparagraph of Directive 2004/27:</i> When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well</p>	<p>The introduction of the concept of the global marketing authorisation again reflects the view developed by the European Court of Justice and the Commission and expressly denies the granting of additional data protection for line extensions.</p>

<p>as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).</p>	
<p><i>Article 11(21) second subparagraph of Directive 2004/27:</i></p> <p>For authorisations under Article 10, those parts of the summary of product characteristics of the reference medicinal product referring to indications or dosage forms which were still covered by patent law at the time when a generic medicine was marketed need not be included.</p>	<p>In the current practice, generic applicants try to obtain two marketing authorisations, one including and one excluding the patented indication. If authorized, the product is then marketed according to the latter SmPC since inclusion of the indication would lead to patent infringement. After the patent has expired, the product is switched to the marketing authorisation including the indication. With the new provision, this complex procedure can be avoided.</p>
<p><i>Article 3 of Regulation 726/2004:</i></p> <p>A generic medicinal product of a reference medicinal product authorised by the Community may be authorised by the competent authorities of the Member States in accordance with Directive 2001/83/EC and Directive 2001/82/EC under the following conditions:</p> <p>(a) the application for authorisation is submitted in accordance with Article 10 of Directive 2001/83/EC or Article 13 of Directive 2001/82/EC;</p> <p>(b) the summary of the product characteristics</p>	<p>Article 3 of the new regulation for centralized procedures breaks the current principle of “son follows father” which restricts the application procedure for generics to be of the same type as that of the reference product. Although representing a substantial facilitation especially for smaller companies, which will not be forced to go through the costly centralized procedure although they do not consider marketing of the product in every member state, the provision still holds up the hardly comprehensible condition of a common name in all member states where the</p>

<p>is in all relevant respects consistent with that of the medicinal product authorised by the Community except for those parts of the summary of product characteristics referring to indications or dosage forms which were still covered by patent law at the time when the generic medicine was marketed; and</p> <p>(c) the generic medicinal product is authorised under the same name in all the Member States where the application has been made. For the purposes of this provision, all the linguistic versions of the INN (international non-proprietary name) shall be considered to be the same name.</p>	<p>application will be filed.</p>
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3 Discussion and Future Aspects

The global pharmaceutical market is a constantly growing market with total sales of 518 billion US\$ and a growth rate of 7% in 2004. Nevertheless, the growth of the world market is slowing down since 5-6 years as it can be seen from the graphical overview in Figure 1a. At the same time, generics have become an integral part of the growth machinery of the pharmaceutical industry in the past years. Figure 1b shows that generic products had a remarkable market share in the US and Canadian market and the big European markets of Germany and UK in 2004. Even more impressive than the actual figures are the growth rates of generic products when compared to the growth rates of brand products which account to 11% versus 6% for the total market and even up to 5-fold in UK (24% vs. 5%) and France (31% vs. 6%). The considerable growth of the generic market was on the one hand pushed by the loss of patent and data protection of blockbuster products like for example Zocor (simvastatin) by Merck & Co, which took not only away business from the original molecule but also from other, patent-protected statins and therefore boosted generic business while obstructing brands in a large line. On the other hand, the acceptance of generics as suitable substitutes for branded medicines has increased substantially by payers, providers and patients

[24]. For example in Germany, the prescription rate of generic medicines has increased from 10.9% in 1981 to 52.2% in 2002 [25]. Nevertheless, the name recognition of generics among patients still bears a large potential for improvement as revealed by a poll sponsored by HEXAL AG and Tomorrow Focus AG. From 1164 respondents, only 31% could define the term “generic” correctly [Source: Focus-Online/HEXAL AG].

Last but not least, the European legislation and its interpretation provided the basis for an eased market access for generic competitors. The definition of essential similarity, the clarification of the prerequisites for abridged applications and of the conditions that allow the application of the proviso by the European Court of Justice not only lead to a bigger legal certainty for generic companies and less possibilities for innovators to challenge marketing authorizations of copycats, but also widened the range of products that can be authorized under the abridged procedure. Furthermore, innovative development and improvement of branded reference products like use of new salts of active compounds or improved pharmaceutical forms have been enabled without the need to provide a complete set of preclinical and clinical data by the generic companies.

Critics of this development contend that with the relaxed regulations, the basic principle of “essential similarity” is left aside and has been changed to “not essentially dissimilar” [26] and that the general considerations of “protection of public health” and “ensuring that innovative firms are not placed at a disadvantage” are being disregarded. Anyway, it should not be ignored that the principle of essential similarity still exists (although not formally named in the new legislation) and that it remains the prerequisite for the classical and undisputable case in which an abridged application can be made without submission of bridging data. What has indeed changed is the band width of products which can be authorized under the abridged procedure although being not essentially similar to the reference product due to for instance bioinequivalence or changes in the active substance, though safe according to the current state of the art. It is noteworthy that without this extension of the application of the abridged procedure, the creation of the legal basis for biosimilar products would have been impossible, since the conditions of essential similarity can hardly be applied on these products due to their complex molecular structure or posttranslational modifications.

If the latter principle is considered by industry and reviewing authorities, the current legislation can very well be understood as a means to ensure public health for several reasons.

As Europe's population grows older and demands for healthcare provision increase, Europe is facing a nightmare scenario of rapidly increasing healthcare costs. One readily available solution to these problems is to be found, in part, in eased access of generic medicines to the pharmaceutical market and in their increased use. By its competitive pricing, which is typically 20% to 80% below that of brand-name originator pharmaceuticals, the use of generics ease the financial burden on the health insurance funds and contribute to a long-term assurance of an adequate medical care of the whole population.

Furthermore, original products often undergo further development and improvement rather than simply being copied by generic companies, a process which is enabled by the experiences gained from the broad medical use of the product until patent expiry. Thus, deficiencies in for example absorption or administration can often be improved and patient compliance is often increased by generic versions.

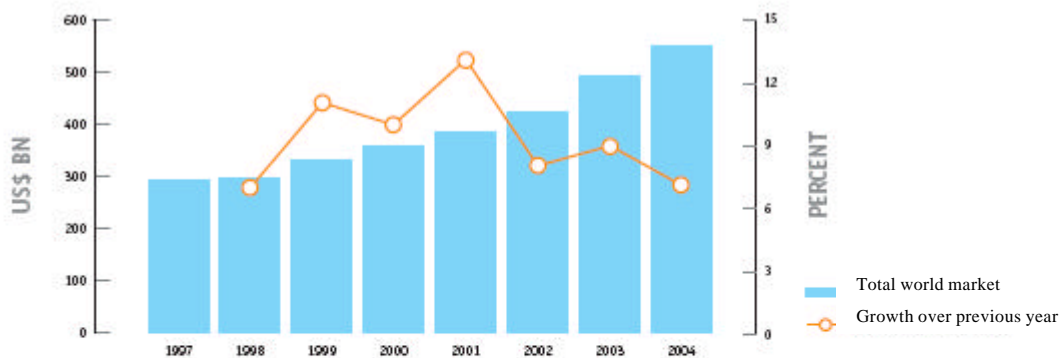
Concerning the rights and intellectual property of the innovative industry, it is to be pointed out that innovators are granted ten years of market exclusivity in the whole EU, which should allow gaining of appropriate profits and what represents a gain of 4 years in countries which so far grant only 6 years of market exclusivity. Furthermore, with the introduction of Regulation No (EEC) 1768/92 on the creation of a Supplementary Protection Certificate for medicinal products (SPC), the decisive role of innovative pharmaceutical research in the continuing improvement in public health was acknowledged as well as the inadequate protection of intellectual property by patent law at that time [27]. In the recitals to Regulation No (EEC) 1768/92 the fear is expressively stated that "medicinal products, especially those that are the result of long, costly research will not continue to be developed in the Community and in Europe unless they are covered by favourable rules that provide sufficient protection to encourage such research" and that "the current situation is creating the risk of research centres situated in the Member States relocating to countries that already offer greater protection". Nevertheless, the restriction of the granted period of supplementary protection to five years and an overall maximum of fifteen years of exclusivity from the first marketing authorization in the Community together with the eased conditions for generic competitors force innovative companies to streamline the development of innovative products in terms of time and costs to keep investment as low as possible and to obtain maximal periods of protection. This surely bears the risk that adverse balanced projects are cancelled earlier or investment is not even made, facts that definitely concern patients suffering from rare conditions and paediatric medicine. Both risks are addressed by the Commission with the introduction of Regulation

(EC) No 141/2000 on orphan medicinal products on one hand, which provides the possibility for incentives granted by the Community or by the Member States to support the research and development of medicinal products for the diagnosis, prevention or treatment of rare diseases [28]. On the other hand, the proposal for a regulation on medicinal products for paediatric use published by the European Commission on 29 September 2004 proposes a wide range of incentives and rewards for innovative as well as generic companies for research and development on paediatric use of known and innovative medicines [29].

Also the innovative industry is reacting and adapting to the new conditions and global competition. In-licensing of R&D products is already common in 30% of R&D projects of the top 20 pharmaceutical companies (Source: IMS Lifecycle) and enables Big Pharma to build franchise more effectively with reduced discovery risk. Moreover, even the largest, most research-focused companies are looking at the generic sector with the latest example being Novartis acquiring the German HEXAL AG and integrating it into the its generic Sandoz division, creating the world leader in the generic drug industry. Innovators are thereby not only taking a piece of the action in the generic market, but are at least partly able to reinvest the profit in the research and development of innovative products. Furthermore, since the lifecycle of innovative products and the profit usually breaks down with the entry of generic versions into the market, R&D is forced to keep up a promising innovative product pipeline ensuring new sources of income.

Looking at the new legislation coming into force in autumn 2005, the rights and possibilities for generic firms are even more strengthened as already discussed above, for example by new rules like the 8+2+1 regulation for the date of abridged application submission and marketing (which on the other hand follows the call for additional protection of innovative therapeutic indications of authorized products) and the newly introduced Bolar clause enabling generic competitors to conduct necessary clinical studies despite patent protection of the reference product. Additionally, with the developing regulations for biosimilar products, the last bastion of the research-based industry is falling.

a)



GLOBAL PHARMACEUTICAL SALES 1997-2004

GLOBAL SALES US\$BN	1997	1998	1999	2000	2001	2002	2003	2004
Total World Market (US\$)	\$289	\$297	\$332	\$357	\$387	\$426	\$493	\$550
Growth over Previous Year (Constant US\$)		7%	11%	10%	12%	9%	10%	7%

b)

Impact of generics on pharmaceutical market

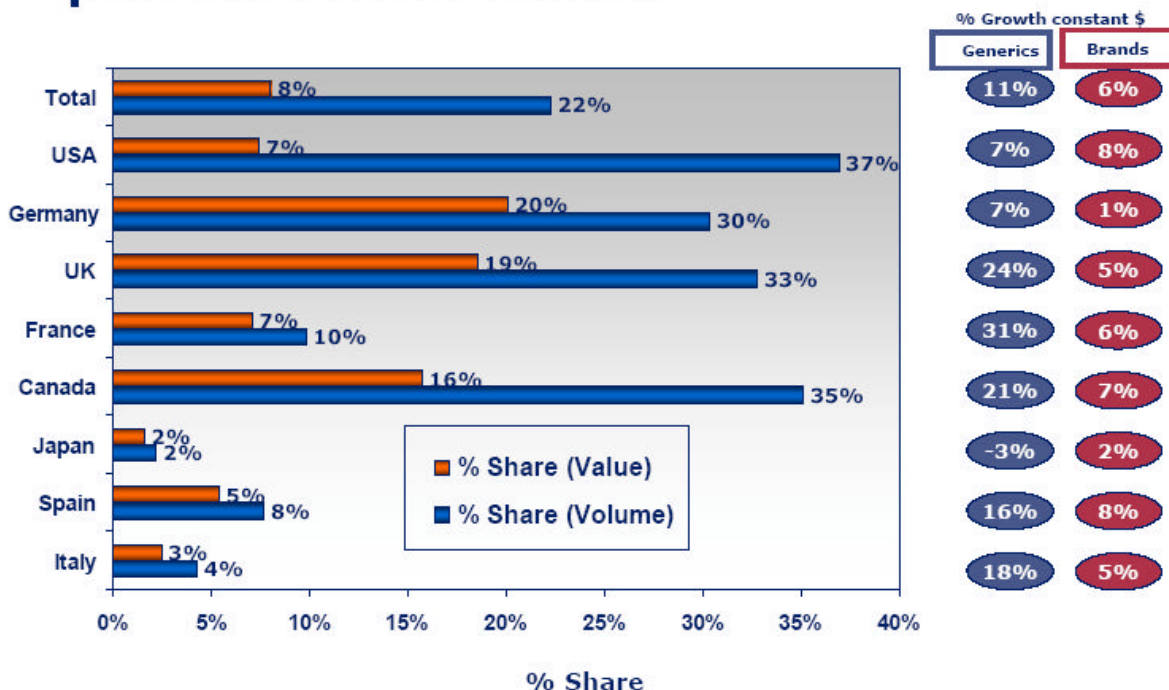


Fig. 1: a) Development of the global pharmaceutical market; b) Share in value and volume of generic products of selected and total market. (Source: IMS MIDAS®, MAT Dec 2004)

The reasons for the European legislative body to steer this obvious course are expressively stated in the Commission's response to the report of G10 Medicines, the high level group on innovation and the provision of medicines set up in 2001 by Commissioners Liikanen and Byrne to establish a new agenda to improve the framework for competitiveness in the pharmaceutical industry and to harness its power to deliver on Europe's health care goals. The group comprised health and industry ministers, pharmaceutical leaders and patient representatives and worked out recommendations addressed at the Commission for the improvement of competitiveness of the industry while meeting important public and social objectives. In its exercise on Competition, Regulation, Access and Availability in Markets, the G10 group focuses amongst other issues on the competitiveness of the generic market and gives the recommendation "To secure the development of a competitive generic market in Europe, that:

- the European Institutions agree a way forward on intellectual property rights issues (especially data exclusivity and Bolar) covered in the Commission's proposed legislation.
- Member States - facilitated by the Commission - explore ways of increasing generic penetration in individual markets (including generic prescribing and dispensing). Particular attention should be given to improved market mechanisms in full respect of public health considerations." [30]

In its response document to the G10 report, the Commission clearly outlines that "It has long been recognised that the European-based pharmaceutical industry plays a critical role in both the industrial and health sectors. It can make a major contribution to the strategic goal, set by the Lisbon Council in 2000, of building the most competitive and dynamic knowledge-based economy in the world, capable of sustainable economic growth with more and better jobs and greater social cohesion". Furthermore, it is realized that the European pharmaceutical industry is declining in competitiveness versus the U.S. and is facing the following problems:

- The European pharmaceutical markets are not competitive enough
- Research and development in the EU is hindered by fragmented research systems and a lack of a coherent and integrated approach between public and private sectors;

– A weak growth in R&D spend: the USA has led the way in developing new technology suppliers and innovation specialists and R&D spending in the USA grew at twice the rate of the EU during the 1990s. [31]

The approach of the Commission for the development of a competitive European-based industry published in the response document encloses among other things the increases of competitiveness of the generic market. As the health care costs across Europe are rising, the increased use of generic medicines is explicitly stated as a means to improve sustainability of financing. The following key actions were defined to face these issues:

- Introduction of a "Bolar-type" provision allowing generic testing, as well as the consequential practical requirements, before the end of the patent protection period in order not to delay the introduction of generics on the market after the expiry of the patent;
- Following political agreement in the Council, the introduction of a marketing authorisation application for a generic and to grant this authorisation in the last two years of the data protection period of the reference product for all products except those falling in the mandatory scope of the centralised procedure (an exception which was not implemented in the new legislation). This will allow these products to come on to the market immediately after the end of the ten years data protection period;
- Providing a clearer Community definition of generics;
- Introducing greater flexibility for generic producers to supply generic medicines to member states where the reference product is not on their market; and
- Addressing the issue of biologically similar products by allowing the production of copies of these products by establishing a clearer regulatory scheme.

All of these key actions were implemented with the introduction of the new legislation and are likely to increase the competitiveness of the European markets in an intracontinental as well as intercontinental way. On the one hand, the eased market access for generic products (8+2+1 regulation, Bolar clause...) and the improved intraeuropean movement of goods (European reference product) might lead to an increased competition between generic and originator firms as well as to increased competition between national European markets. Furthermore, with the introduction of the Bolar clause, the European location becomes more attractive and susceptible for the development and clinical testing of generic medicines, which

might in part keep generic companies from developing and testing their products in non-patent (and low-priced) countries in Eastern Europe and India.

On the other hand, with the introduction of a legal basis for the authorisation of biosimilar products and the drafting of overarching and product-specific guidelines on quality, safety and efficacy issues, Europe is clearly one step ahead the U.S in this sector. While the first biosimilar applications are already submitted to the EMEA in 2005 (e.g. human growth hormone Omnitrope by Sandoz) and approvals are awaited for 2007, the U.S. is still struggling with the determination of which of its laws, namely the Food, Drug and Cosmetic Act or the Public Health Service Act, should be used to authorise these products.

Although presenting a substantial progress for the generic business, some issues still remain high hurdles for the authorisation and marketing of generic products. The Bolar clause for example leaves uncovered the production and stock-piling of commercial batches until patent expiry, which therefore has to be further on performed in non-patent countries.

Another aspect concerns mainly biosimilar products, which are forced to authorization via the centralized procedure as Part A products. Several issues about the naming of these products remain unsolved since the duty to chose one European product name might interfere with national pricing and reimbursement policies for (bio)generics. Further guidance and clarification on this issue by the EMEA is awaited for the end of 2005.

Another hurdle for the fast and uniform penetration of the European market is for example the problem of non-harmonised originator SmPCs which still forces generic companies to market their products with the smallest common nominator of indications and the biggest number of contra-indications. But when reading the text of the new Directive 2004/27, a vague foreboding might raise that the stamina of issues like this might be tested again by the Court.

Besides all these advantages for the generic industry, it is also recognized by the Commission that although generics can provide significant savings for healthcare providers, their use must be balanced with sufficient incentives to develop innovative products. The above mentioned regulation for orphan drugs and paediatric medicines encourage investment in less profitable sectors. Furthermore, guidance for innovative methods of treatments like gene therapy, cell therapy and tissue engineering were currently published by the European Commission [32].

In its new EU industrial policy, the European Commission is initiating further steps to enhance the competitiveness in the pharmaceutical sector. At the annual meeting of the European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels in June 2005, enterprise commissioner Günther Verheugen presented the actual strategy which

includes the 7th Research Framework Programm and the Competitiveness and Innovation Programm. To re-establish Europe's R&D leadership in the strategic biopharmaceutical sector, a significant increase in spending has been proposed by the Commission. According to the Commission proposal €73.2 billion should become available to the 7th European Research Framework Programme. Life Sciences and Biotech are thought to significantly benefit from the planned increase, annual contributions earmarked for life sciences are to be more than doubled. One important part of the R&D Framework Programme are Technology Platforms. The objective of this new instrument is to foster public-private partnerships at the European level and bring together academia, industry, Member States and the Commission to pool Europe's limited resources in order to create added value. Its main objective is to enhance and accelerate the development process of medicines so as to ensure the rapid application of scientific breakthroughs [33]. Besides this, the commission looks again at how to allow the industry more flexibility in establishing prices and to improve the access of public to information on pharmaceuticals.

Despite price erosions and uncertainties over biogenerics (especially in the U.S.), IMS Health forecasts that the world wide generic growth will be 10-15% or \$66 billion to \$82 billion in 2009. It is to be expected that the European legislation will be further opened to increase generic penetration while Europe's attractiveness for innovative business and the competitiveness to the U.S. market have to be further promoted. But besides all political and economical strategies, one must not forget the aim of protection of public health which must be fairly balanced by Authorities and industry with political and economical motivations.

4 Summary

The term “essential similarity” was introduced in the European legislation as a basic principal for applications under the abridged procedure and defined the conditions under which a second applicant can refer to the preclinical and clinical data of the reference product. Due to the initial lack of a detailed definition of the conditions under which a second product can be considered essentially similar to its reference product, a long history of legal proceedings between innovator companies seeking for protection of their data and their position in the market and generic companies aiming at quick market entry combined with low investment for research and development commenced.

In the present thesis, an overview of the development of the pharmaceutical market with its almost unlimited possibilities for copycats of original products to be marketed before the introduction of a common European legal basis is given. With the implementation of Directive 65/65/EEC, not only the obligatory submission of results of physico-chemical, biological or microbiological tests, preclinical tests and clinical trials with the application for marketing authorisation was introduced, but also exemptions for second applicants which were further defined by the introduction of the principal of “essential similarity” with Directive 87/21/EEC. With the description and discussion of four important law cases of the European Court of Justice, the resulting definition of “essential similarity” and the extension of the applicability of the abridged procedure to products that are not essentially similar to their reference product are presented. It could be shown that although the term “essential similarity” will disappear with the implementation of the new pharmaceutical legislation in autumn 2005, it remains the prerequisite for the classical and undisputable case in which an abridged application can be made without submission of bridging data, but lost its status as a dogma for generic applications. Together with additional pro-generic provisions, the new legislation represents a boost for the generic industry and is likely to lead to an increased market penetration by generic products while seeking for compensation and incentives for innovative companies.

Finally, it is shown that the pro-generic course of the European Commission can be understood as a means to enhance competitiveness and innovation in the pharmaceutical sector and is part of the European strategy to strengthen the position of the European pharmaceutical market in comparison to the US market.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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